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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,920	07/11/2005	John K. Leach	019028-56312	6179
7590 Ronald I Eisenstein Nixon Peabody 100 Summer Street Boston, MA 02110		08/31/2007	EXAMINER AFREMOVA, VERA	
			ART UNIT 1657	PAPER NUMBER
			MAIL DATE 08/31/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/521,920

Applicant(s)

LEACH ET AL.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION:

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 1/20/2005; 10/10/2006.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Clams 1-8 (preliminary amendment 1/20/2005) are pending and under examination.

Claim Rejections - 35 USC § 112

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the reactive species" as second agent in a method for culturing primary hepatocytes. There is insufficient antecedent basis for this limitation in the claim. The scope of "the reactive species" is a broader than the previously recited narrow limitations "reactive oxygen" and "reactive nitrogen species" within the same claims and, thus, is considered indefinite since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. MPEP 2173.05(c). In alternative, inhibitor of "reactive species" is an anti-oxidant and, thus, the concept of using two different agents is unclear and uncertain as claimed since they are the same agents capable of the same function.

Chemical name of the presently claimed glutathione precursor compound such as "2-oxo-thiazolidine" is incorrect and/or indefinite in the lack of specific definitions in the as-filed specification because 14 different compounds incorporate "2-oxo-thiazolidine" group (see STN file Registry). Thus, it is unclear what compounds are used in the culture of hepatocytes as intended. Chemical name of the presently claimed "NG-methylarginine" is also incorrect and/or indefinite. The lack of proper chemical names adds to uncertainty about the differences between first agent and second agent particularly in view that the claimed chemicals including tocopherol

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succinate, mannitol, "2-oxo-thiazolidine" and "NG-methylarginine are identified as being both agents (see claims 2 and 7 and see claims 3 and 8).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. (Cancer Research. 1994, 54 (2): 5848-5855).

Claims are directed to a method for culturing primary hepatocytes comprising one step of plating or culturing primary hepatocytes in the presence of two agents wherein first agent is anti-oxidant and second agent that inhibits the reactive species or increases intracellular glutathione, wherein said primary hepatocytes maintain function for at least five days. Some claims are further drawn to culturing primary hepatocytes in the presence of anti-oxidant such as tocopherol succinate. Some claims are further drawn to culturing primary hepatocytes in the presence the second agent that increases intracellular glutathione or "glutathione precursor".

US 5,198,432 (Fariss) discloses a method for culturing primary hepatocytes in Waymouth's medium (col.7, line 36) supplemented with antioxidant vitamin E including tocopherol succinate for 5-7 days (col. 14, lines 20-27). The Waymouth's medium contains vitamins or antioxidants that are inhibitors of "reactive species within the broadest meaning of

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the claims (see ATCC catalogue page 525). The Waymouth's medium also contains folic acid that is an agent that increases intracellular glutathione as evidenced by Sharma et al. (page 5852). Thus, the method of US 5,198,432 (Fariss) for culturing primary hepatocytes comprises culturing primary hepatocytes in the presence of 2 agents within the broadest meaning of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,198,432 (Fariss) in the light of evidence by ATCC catalogue and Sharma et al. (Cancer Research. 1994, 54 (2): 5848-5855) taken with Pourahmad et al.(IDS reference), Dilworth et al. (IDS reference) and Roberts et al. (IDS reference).

Claims are directed to a method for culturing primary hepatocytes comprising one step of plating or culturing primary hepatocytes in the presence of two agents wherein first agent is anti-oxidant and second agent is a) a functional inhibitor of an enzyme that generates reactive oxygen and reactive nitrogen species or b) an agent that directly inhibits the reactive species, or c) an agent that increases intracellular glutathione, wherein said primary hepatocytes maintain function for at least five days. Some claims are further drawn to culturing primary hepatocytes in the presence of anti-oxidant such as tocopherol succinate or mannitol. Some claims are further drawn to culturing primary hepatocytes in the presence the second agent such as glutathione

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precursor or "2-oxo-thiazolidine". Some claims are further drawn to culturing primary hepatocytes in the presence of the second agent such as inhibitor of nitric oxide or "NG-methylarginine". Some claims are further drawn to culturing primary hepatocytes in the presence of "2-oxo-thiazolidine" and tocopherol succinate as first and second agents. Some claims are further drawn to culturing primary hepatocytes in the presence of "NG-methylarginine" and mannitol as first and second agents.

US 5,198,432 (Fariss) teaches protective effects of antioxidants including tocopherol succinate on lifespan of cultures of primary hepatocytes. The cited method is relied upon as explained above for culturing primary hepatocytes includes the use of Waymouth's medium supplemented with antioxidants or vitamins including tocopherol succinate and with agent increasing intracellular glutathione or folic acid as evidenced by ATCC Catalogue (page 525) and by Sharma et al. (page 5852). The culture medium in the method of US 5,198,432 does not contain 2-oxo-thiazolidine, methylarginine and mannitol as first and/or second agents.

However, the references teach protective effects of the presently claimed agents including mannitol (Pourahmad et al.), 2-oxo-thiazolidine (Dilworth et al.) and methylarginine (Roberts et al.) on cultures of hepatocytes, for example: see abstract of the cited references.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to incorporate protective agents including the presently claimed tocopherol succinate, 2-oxo-thiazolidine, methylarginine and/or mannitol in the culture of primary hepatocytes with a reasonable expectation of success in maintaining viability of hepatocytes because the presently claimed agents have been known and used for culturing and maintaining viability of hepatocytes as adequately demonstrated by the cited references.

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combined. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

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August 28, 2007

A handwritten signature in black ink, appearing to read 'V. Afremova', with a long horizontal flourish extending to the right.

VERA AFREMOVA

PRIMARY EXAMINER